Allergy-Like Immediate Reactions with Herbal Medicines: A Retrospective Study Using Data from VigiBase(®)

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Abstract: INTRODUCTION Herbal medicines are used worldwide and with an increasing popularity in Western countries. Although often perceived as 'naturally safe', herbals may cause severe adverse drug reactions (ADRs), with immediate allergic reactions being particularly life threatening. OBJECTIVES The aim of this study was to analyse immediate allergy-like ADRs to herbals documented in VigiBase(®), the WHO international pharmacovigilance database. METHODS The documentation of all suspected ADRs in association with herbal exposure reported to VigiBase(®) from 1969 to August 2014 was retrieved. Among all reports in which WHO-ART reaction terms were indicative of acute allergic reactions, those classified as 'suspect' with a documented causality assessment and latency time of 1 day were selected. For the most frequent specific herbal-ADR combinations, the information component (IC) as a measure of disproportionality based on Bayesian statistics was calculated. RESULTS We identified 757 reports out of 1039 ADRs. Products with mixed herbals (36.0 %) as well as those administered orally (63.2 %) were predominant. The most frequent reactions were urticaria and rash (49.2 %). Anaphylactic reactions accounted for 9.5 %. Disproportionally frequent reporting of mouth edema (IC = 1.81) and anaphylactic reactions (IC = 1.24) to Phleum pretense were noted. CONCLUSION Our findings indicate that herbal medicines for oral use carry a risk of causing immediate allergy-like ADRs. Studies using the Vigibase(®) database can identify specific combinations of particular herbs and adverse reactions. Healthcare professionals and patients should be aware of these risks and report any serious adverse experiences.

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ORIGINAL ARTICLE

Allergy-like immediate reactions during the use of herbal remedies as reported in VigiBase®

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Abstract

Background: Herbal remedies are used worldwide and with an increasing popularity in Western countries. Although often perceived as "naturally safe", herbals may cause severe adverse drug reactions (ADR), and particularly immediate-type allergic reactions can be life threatening.

Objectives: Analyses of allergy-like immediate ADR to herbals documented in VigiBase®, the WHO international pharmacovigilance database.

Methods: All suspected ADR in association with herbal exposure reported to VigiBase® from 1969 to August 2014 were retrieved. Among those all reports where WHOART reaction terms were indicative of acute allergic reactions, classified as "suspect" with a documented causality assessment and latency time of ≤1 day were selected. For the most frequent specific herbal-ADR combinations the information component (IC) as a measure of disproportionality based on Bayesian statistics was calculated.

Results: We identified 757 reports with 1,039 ADR. Products with mixed herbals (36.0%) and oral administration (63.2%) were predominant. The most frequent reactions were urticaria and rash (49.2%). Anaphylactic reactions accounted for 9.5%. We found disproportionally frequent reporting of mouth oedema (IC=1.81) and anaphylactic reactions (IC=1.24) with *Phleum pratense*.

Conclusion:

Our findings indicate that herbal medicines for oral use carry a risk for allergy-like immediate ADR. Studies using the Vigibase® database can identify specific combinations of particular herbs and adverse reactions. Health care professionals and patients should be aware of these risks and report any serious adverse experiences.

Keywords

adverse drug reactions, allergy, hypersensitivity, drug safety, herbal medicine, pharmacovigilance, phytotherapy.

Key messages

- While herbal products for oral use are generally regarded as safe, international pharmacovigilance data indicate that many such products carry a risk for acute allergy-like adverse reactions.
- The recognition of the occurrence of such reactions with specific products is needed for their timely diagnosis as well as for prevention.

1 Introduction

There is an increased prevalence in use of herbal medicines among the adult population in many western countries [1-3]. The most recent 2012 US National Health Interview Survey showed that 18% of adults used natural products including herbal medicine during the past 12 months [3]. The public often considers herbal products as safe since they are natural and is unaware that Complementary and Alternative Medicines (CAM) are not tested by regulatory agencies for their safety and efficacy [4]. In most countries, herbal medicines are defined as dietary supplements and as such do not have to meet pre- and postmarketing drug policy regulations [5]. However, use of herbal medicines can be associated with development of severe adverse reactions as a result of complex chemistry of herbals as well as their inappropriate use and a lack of quality control [6, 7]. In addition, patients may not disclose self-medication with herbal medicines to their health care professionals, and even if they do there may be limited knowledge of their potential adverse reactions and interactions with concomitantly used prescription drugs [8, 9].

In the absence of comprehensive systematic safety evaluations of herbal medicines, spontaneous reporting systems of adverse drug reactions (ADR) play a major role for their worldwide safety surveillance and signal detection [10]. Although there are many case reports of ADR associated with herbals in the literature, the majority of reports are documented in large pharmacovigilance databases, and those valuable resources should be systematically analyzed for ADR associated with herbals [7, 11, 12]. ADR to herbals cover a wide range of manifestations that are mostly mild and followed by full recovery. However, immediate-type allergic reactions are also a typical, potentially life threatening and therefore clinically most relevant adverse reaction to herbal products. Therefore, we conducted a study that aimed to investigate the reporting patterns and characteristics of immediate allergic adverse reactions associated with herbal medicines in international pharmacovigilance.

2 Methods

2.1 Study settings

VigiBase®, the largest international pharmacovigilance database of spontaneous ADR reports was the source of our reports. VigiBase® is maintained by the Uppsala Monitoring Centre (UMC) in association

with the World Health Organization's (WHO) international pharmacovigilance program. The UMC is an independent foundation and a center for international service and scientific research. It collaborates with 118 member countries around the world that collect and evaluate spontaneous ADR reports [13]. These centers forward anonymized ADR reports received from various primary reporting sources to the UMC in a standardized format, containing structured information on adverse events, involved patients and drugs including standardized semi-quantitative causality assessments [14].

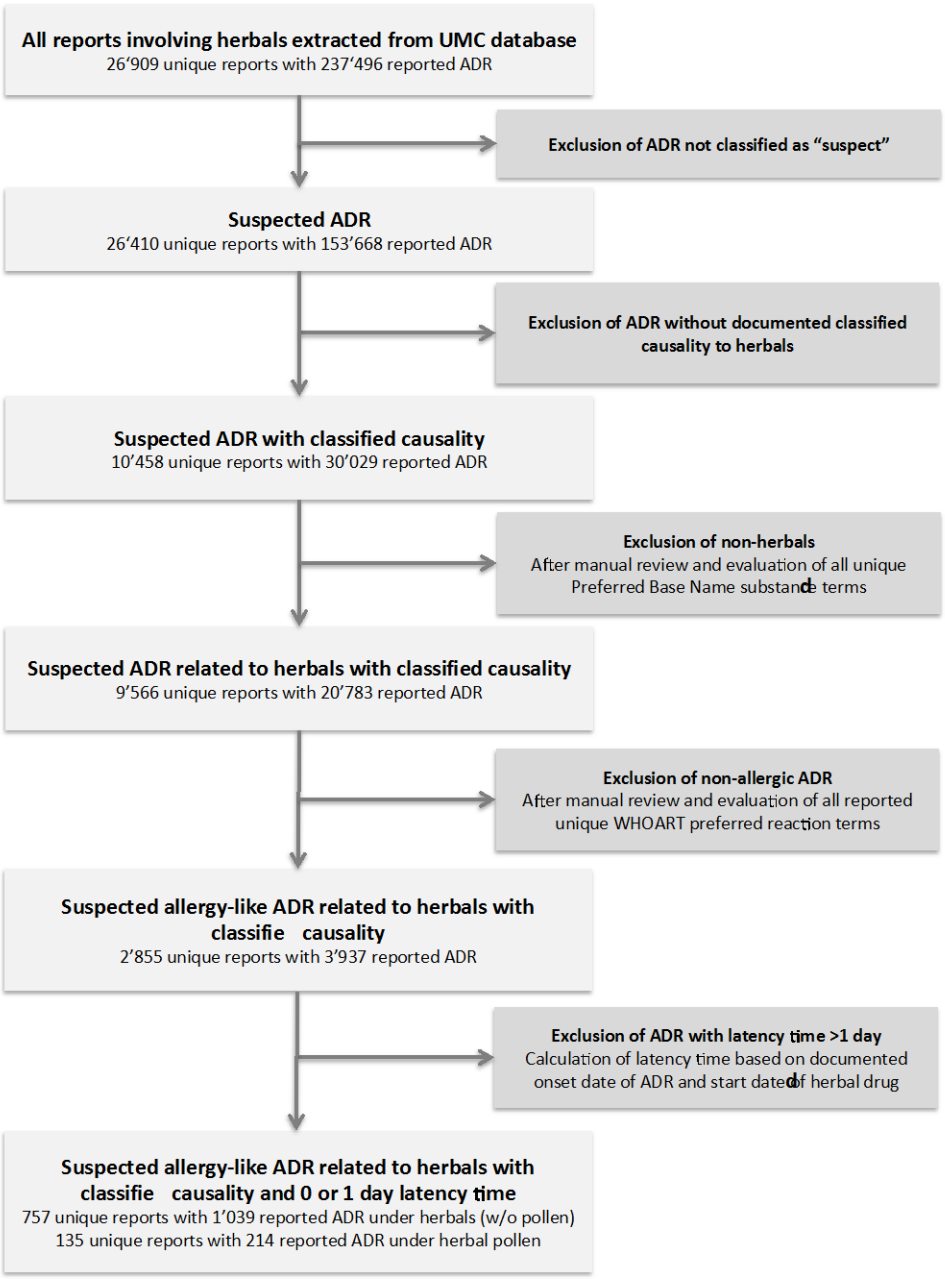
The database of the UMC, Vigibase currently contains over 9 million case reports. The WHO Adverse Drug Reaction Terminology (WHOART) and WHO Drug Dictionary/WHO Herbal Dictionary are used for coding of clinical information in relation to drug therapy and reported drugs on the reports [13]. MedDRA terminology has been made the standard in VigiBase for several years, and there are automated algorithms that convert codes form those two dictionaries in both directions. Herbal medicine refers to herbs, herbal materials, herbal preparations and finished herbal products. Herbal products are assigned herbal anatomical-therapeutic-chemical (HATC) codes specifying their therapeutic use according to the Guidelines for Herbal ATC classification [15]. HATC classification aggregates herbal remedies according to their medical uses that have been found in the literature and does not indicate that the remedy has been proven as effective or safe [13]. Herbal pharmacovigilance terminology is used in accordance with WHO guidelines [16].

2.2 Study design and selection of cases

A flowchart of the study design and case selection process is presented in Fig. 1. The aim of our study was to focus on immediate-type allergic ADR associated with herbals, because those are potentially life threatening and therefore clinically highly relevant. The level of documentation within VigiBase® is heterogeneous, and it may be difficult to make an exact medical diagnosis based on the available information. With this limitation in mind we defined case selection criteria that are likely indicators of immediate-type allergic reactions (see Table 2 for a listing of included WHOART terms). Because VigiBase® does not allow for a validation of type 1 immediate hypersensitivity reactions according to comprehensive clinical diagnostic criteria we carefully refer to included cases as "allergy-like immediate reactions" in our study. For inclusion in the study population we used the following inclusion criteria:

exposure to manually validated herbal products, which must be classified by the primary reporter as "suspect" with regard to the reported ADR; documented causality assessment between herbal product and ADR classified as "possible", "probable" or "certain"; documented latency time from herbal exposure to ADR onset of no more than one day; manual selection of WHO-ART preferred terms indicating an ADR that is a likely symptom of an immediate-type hypersensitivity reaction. In contrast, reaction terms that are compatible with but have a low specificity for immediate type allergic reactions such as cough, dyspnea, larynx pain, gastrointestinal symptoms or pruritus were on their own not considered sufficient for inclusion. Furthermore, we excluded ADR associated with the HATC term "herbal pollen not otherwise specified" from the main analysis because these are likely to refer to desensitization vaccines for the treatment of pollen allergies (ADR that may have a distinct special relationship to the indication for the suspected herbal products). ADR were also stratified over asthma-like reactions (defined by WHO-ART preferred terms "asthma", "stridor" or "bronchospasm") vs. all other ADR terms with high specificity for immediate-type allergic reactions.

Fig. 1: Flowchart of study design and case selection process



2.3 Statistical analysis

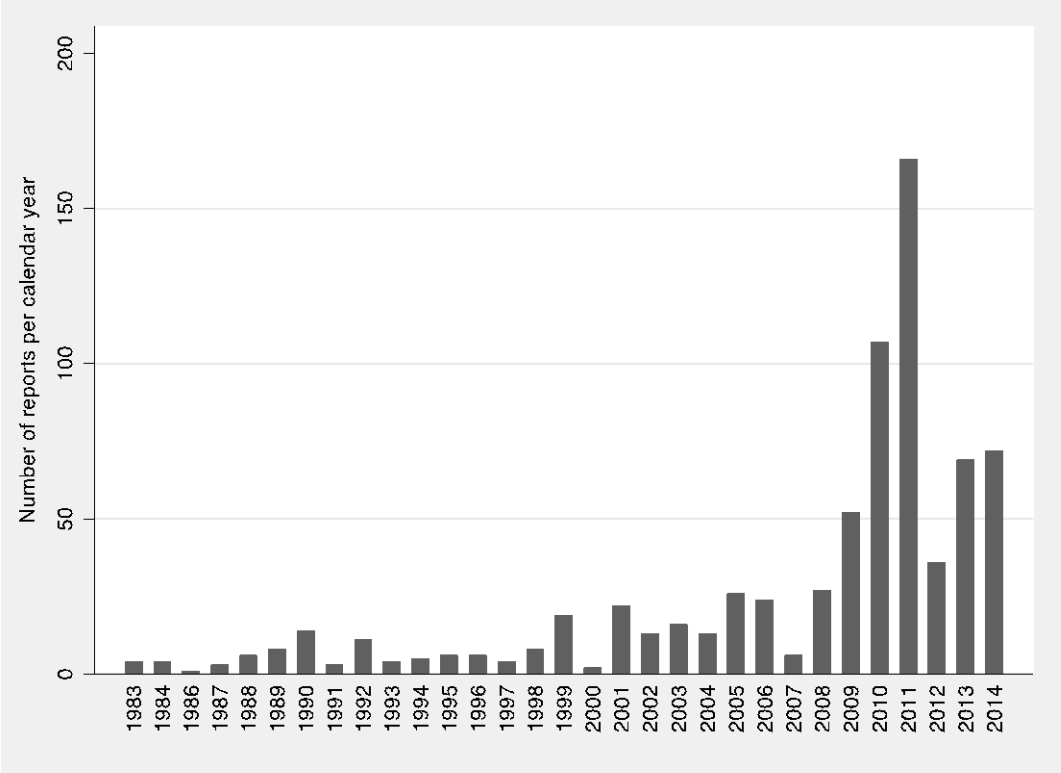
Descriptive statistics was used to analyze case report characteristics. The unexpected ADR to herbals was quantitatively analysed using the Bayesian Confidence Propagation Neural Network methodology (BCPNN), a data-mining technique used for the detection of new signals in spontaneous reporting of ADR [17]. The measure of disproportionality expressed as the Information Component (IC) is used to indicate the frequency of specific drug-ADR combination that occurs more frequently in the database than expected in relation to the number of all reports with the particular drug and ADR and the total number of reports in the database. The IC is a logarithmic measure of association and is calculated as $IC = \log_2 p(x,y) / (p(x) * p(y))$, where: $p(x)$ = probability of a specific drug x is listed on a case report; $p(y)$ = probability of a specific drug-ADR combination x and y is listed on a case report; $p(x,y)$ = probability of a specific drug x is listed on a case report.

An IC of 0 results from drug-ADR combinations for which the number of observed cases is the same as that which might be expected from the overall reporting in the data set. Accordingly, an IC above 0 indicates that a specific drug-ADR combination occurs more frequently in the dataset than expected from the background of the database. For the IC analysis we used the dataset of all reports that met our inclusion criteria and calculated the IC for all specific combinations that occurred with a frequency of 10 or more. Data management and analyses were performed using STATA Version 13.1 (StataCorp LP, College Station, TX, USA).

3 Results

The initial dataset extracted from VigiBase® comprised 26,909 unique ADR reports with documented exposure to herbal products. These reports were received between 1969 and August 2014. After application of exclusion criteria 757 unique reports remained with 1,039 ADR (more than one reaction term can be reported per case) related to herbal products for the analyses (Fig. 1). The chronology for receipt of those reports is presented in Fig. 2, showing a pronounced increase of the reporting frequency in recent years. More than 50% of all included reports came from only three countries, i.e. Germany (22.3%), Australia (14.9%) and Thailand (11.2%). The most frequent primary reporters were physicians (32.1%), followed by hospitals (24.7%) and pharmacists (14.1%).

Fig. 2: Reporting frequency over time for all 757 included cases with allergy-like immediate adverse reactions during the use of herbals



3.1 Patients' characteristics

Patient demographics and reporting information of the 757 included reports are presented in Table 1. Women were overrepresented among included cases (68.6%), and more than one third of cases fell into the age category from 18 to 44 years.

Table 1: Demographics of unique reports/patients of allergy-like immediate adverse reactions during the use of herbal remedies (N=757)

	n	%
Gender		
Female	519	68.6
Male	225	29.7
Not specified	13	1.7
Age group (years)		
<18	109	14.4
18 - 44	278	36.7
45 - 64	199	26.3
≥ 65	117	15.5
Not specified	54	7.1
Reporting country		
Germany	169	22.3
Australia	113	14.9
Thailand	100	13.2
South Korea	49	6.5
Spain	43	5.7
Sweden	39	5.2
Switzerland	37	4.9
Cuba	29	3.8
United Kingdom	17	2.3
Malaysia	16	2.1
New Zealand	15	2.0
Norway	11	1.5
Other (<10 reports per country)	119	15.7
Reporting source		
Physician	243	32.1
Hospital	187	24.7
Pharmacist	107	14.1
Manufacturer	38	5.0
Consumer / non health professional	14	1.9
Other / not specified	168	22.2

3.2 Allergy-like immediate reactions

Characteristics of allergy-like immediate reactions under herbal remedies are presented in Table 2 along with stratifications over the three given causality categories. The likelihood of a causal connection in the 1,039 reported ADR had been assessed as “possible”, “probable” and “certain” in 59.2%, 32.2% and 8.6%, respectively. Outcome was favorable with recovery in 77.7% of all ADR, and there were no lethal cases. One should note however that there was no information available on the outcome for 9.2%. Asthma-like reactions accounted for only 4.8% of all ADR. The most commonly reported allergy-like immediate adverse reactions associated with herbals were “rash” (16.2%), “urticaria” (15.3%) and “rash erythematous” (13.4%). Anaphylactic and anaphylactoid reactions accounted altogether for 9.5% of reported ADR (anaphylactic reaction 4.5%, anaphylactic shock 2.8%, anaphylactoid reaction 2.2%), and Table 2 shows other serious ADR such as bronchospasm or larynx oedema.

Table 2: Characteristics of allergy-like immediate reactions during the use of herbal remedies (N=757)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	n	%	n	%	n	%
Total number of reported ADR	**615**	**59.2**	**335**	**32.2**	**89**	**8.6**	**1039**	**100**
Outcome								
Recovered	431	70.1	296	88.4	80	89.9	807	77.7
Not recovered (yet)	97	15.8	18	5.4	4	4.5	119	11.5
Recovered with sequelae	10	1.6	7	2.1	-	-	17	1.6
Died	-	-	-	-	-	-	-	-
Unknown / Not specified	77	12.5	14	4.2	5	5.6	96	9.2
Type of ADR [a]								
Allergic	584	95.0	319	95.2	86	96.6	989	95.2
Asthma-like	31	5.0	16	4.8	3	3.4	50	4.8
Specification of reported ADR [a] (WHOART [b] preferred term)								
Rash	108	17.6	53	15.8	7	7.9	168	16.2
Urticaria	86	14.0	57	17.0	16	18.0	159	15.3
Rash erythematous	91	14.8	37	11.0	11	12.4	139	13.4
Allergic reaction	42	6.8	13	3.9	3	3.4	58	5.6
Angioedema	27	4.4	21	6.3	5	5.6	53	5.1
Flushing	29	4.7	15	4.5	4	4.5	48	4.6
Anaphylactic reaction	28	4.6	10	3.0	9	10.1	47	4.5
Face oedema	34	5.5	10	3.0	2	2.3	46	4.4
Rash maculo-papular	23	3.7	21	6.3	-	-	44	4.2
Oedema mouth	14	2.3	14	4.2	10	11.2	38	3.7
Oedema periorbital	24	3.9	9	2.7	3	3.4	36	3.5
Anaphylactic shock	11	1.8	15	4.5	3	3.4	29	2.8
Bronchospasm	14	2.3	11	3.3	1	1.1	26	2.5
Anaphylactoid reaction	11	1.8	8	2.4	4	4.5	23	2.2
Tongue oedema	12	2.0	6	1.8	3	3.4	21	2.0
Asthma	11	1.8	5	1.5	2	2.3	18	1.7
Dermatitis contact	5	0.8	8	2.4	3	3.4	16	1.5
Dermatitis	6	1.0	7	2.1	1	1.1	14	1.4
Oedema pharynx	4	0.7	6	1.8	1	1.1	11	1.1
Oedema generalised	5	0.8	4	1.2	-	-	9	0.9
Eosinophilia	8	1.3	-	-	-	-	8	0.8
Allergy	6	1.0	-	-	1	1.1	7	0.7
Larynx oedema	4	0.7	3	0.9	-	-	7	0.7
Stridor	5	0.8	-	-	-	-	5	0.5
Erythema multiforme	3	0.5	-	-	-	-	3	0.3
Skin reaction localised	2	0.3	-	-	-	-	2	0.2
Bronchospasm aggravated	1	0.2	-	-	-	-	1	0.1
Drug hypersensitivity syndrome	-	-	1	0.3	-	-	1	0.1
Purpura allergic	-	-	1	0.3	-	-	1	0.1
Urticaria acute	1	0.2	-	-	-	-	1	0.1

[a] ADR, adverse drug reactions; [b] WHOART, The WHO Adverse Reactions Terminology

3.3 Suspect Herbals

Descriptions of specific herbals associated with reported ADR and their route of administration are presented in Table 3. Preparations that contained a mixture of several herbals were the suspected cause in 36% of all ADR and therefore by far the most frequently reported herbal products in association with ADR, followed by *Phleum pratense* (common name: *Timothy grass*, 6.5%), *Andrographis paniculata* (several common names including kalmegh, 5.0%), Echinacea purpurea (3.8%) and *Ginkgo biloba* (3.6%). Oral administrations accounted for almost two thirds of ADR, followed by topical / cutaneous and sublingual administrations in 9.0% and 6.4%, respectively.

Table 3: Characteristics of administered herbal remedies associated with allergy-like immediate reactions (N=757)

	Causality						Overall	
	Possible		Probable		Certain			
	n	%	n	%	n	%	n	%
Total number of reported ADR [a]	**615**	**59.2**	**335**	**32.2**	**89**	**8.6**	**1039**	**100**
Herbs reported in association with ADR [a]								
Mixed herbals	220	35.8	126	37.6	28	31.5	374	36.0
Phleum pratense	16	2.6	25	7.5	27	30.3	68	6.5
Andrographis paniculata	27	4.4	25	7.5	-	-	52	5.0
Echinacea purpurea	30	4.9	6	1.8	3	3.4	39	3.8
Ginkgo biloba	29	4.7	6	1.8	2	2.3	37	3.6
Hedera helix	25	4.1	4	1.2	1	1.1	30	2.9
Plantago ovata	6	1.0	9	2.7	4	4.5	19	1.8
Hypericum perforatum	13	2.1	4	1.2	1	1.1	18	1.7
Viscum album	13	2.1	4	1.2	1	1.1	18	1.7
Valeriana officinalis	10	1.6	6	1.8	1	1.1	17	1.6
Cimicifuga racemosa	11	1.8	5	1.5	-	-	16	1.5
Mentha x piperita	6	1.0	9	2.7	1	1.1	16	1.5
Other (<15 ADR per herbal)	209	34.0	106	34.0	20	22.5	335	32.4
Administration route of reported herbal								
Oral	394	64.1	234	69.9	29	32.6	657	63.2
Topical / cutaneous	57	9.3	26	7.8	10	11.2	93	9.0
Sublingual	18	2.9	21	6.3	27	30.3	66	6.4
Intravenous	29	4.7	6	1.8	4	4.5	39	3.8
Subcutaneous	11	1.8	12	3.6	6	6.7	29	2.8
Other (≤10 ADR per route)	38	6.2	14	4.2	6	6.7	58	5.6
Not specified	68	11.1	22	6.6	7	7.9	97	9.3

[a] ADR, adverse drug reactions

3.4 Disproportionality analysis

Calculations of IC values for all 16 specific herbal / allergy-like reaction combinations that had been reported at least 10 times are presented in Table 4. Accordingly, significantly higher frequencies than expected by chance were found for *Phleum pratense* (Timothy grass) linked to oedema of the mouth (IC= 1.81, 95%CI 0.67-2.86) and to anaphylactic reactions (IC= 1.23, 95%CI 0.03-2.33).

Table 4: Most frequently reported (N≥10) specific combinations of herbal remedies and allergic reactions with their IC values

Herbal remedy	**WHOART [b] preferred term**	**N reports**	**%**	**IC [a]**	**(95% CI)**
Mixed herbals	Rash	75	(7.2)	-0.15	(-0.60 - 0.30)
Mixed herbals	Urticaria	58	(5.6)	-0.44	(-0.93 - 0.04)
Mixed herbals	Rash erythematous	36	(3.5)	-0.93	(-1.53 - -0.36)
Mixed herbals	Face oedema	21	(2.0)	-0.11	(-0.95 - 0.68)
Mixed herbals	Allergic reaction	20	(1.9)	-0.52	(-1.35 - 0.26)
Mixed herbals	Rash maculo-papular	20	(1.9)	-0.12	(-0.98 - 0.70)
Mixed herbals	Oedema mouth	19	(1.8)	0.02	(-0.88 - 0.87)
Mixed herbals	Anaphylactic reaction	15	(1.4)	-0.63	(-1.59 - 0.26)
Mixed herbals	Angioedema	15	(1.4)	-0.80	(-1.76 - 0.07)
Mixed herbals	Flushing	15	(1.4)	-0.66	(-1.62 - 0.22)
Mixed herbals	Anaphylactoid reaction	12	(1.2)	0.08	(-1.08 - 1.16)
Phleum pratense	Oedema mouth	12	(1.2)	**1.81**	**(0.67 - 2.86)**
Andrographis paniculata	Urticaria	11	(1.1)	0.01	(-1.11 - 1.01)
Mixed herbals	Oedema periorbital	11	(1.0)	-0.69	(-1.83 - 0.33)
Mixed herbals	Anaphylactic shock	10	(1.0)	-0.52	(-1.74 - 0.58)
Phleum pratense	Anaphylactic reaction	10	(1.0)	**1.24**	**(0.03 - 2.33)**

[a] IC, information component; [b] WHOART, The WHO Adverse Reactions Terminology

4 Discussion

We report on a series of 757 case-reports indicative of allergy-like adverse reactions during the use of herbal remedies from the Vigibase of spontaneous ADR reports coming from 42 countries since 1969. Our study documents that a large number of different herbal remedies cause immediate allergy-like reactions in the population. Among all reports, mixed herbals, *Phleum pratense* and *Andrographis paniculata* were most frequently reported in association with ADR. *Andrographis paniculata* is well known in Ayurveda medicine and typically used for the treatment of common cold. Previously reported findings from Thailand investigating the safety of *Andrographis paniculata* showed a similar range of hypersensitivity reactions ranging from skin reactions to anaphylaxis [18]. Case-reports indicative of hypersensitivity to other most frequently reported herbals in our study have been published previously [19-24].

High proportion of reports concerned women between the age of 18 and 44. The most frequently reported manifestations of allergy-like immediate reactions were skin reactions, and also anaphylactic / anaphylactoid reactions most frequently observed after oral administration. Such severe ADR are rarely seen after oral use of herbals. The occurrence of allergic reactions is rather more likely to be expected after cutaneous and mucosal exposure, a known risk factor for sensitization to allergens. It is reasonable to assume that rather easy to diagnose reactions with a short time to onset and skin manifestations as well as serious reactions are more frequently reported compared to other reactions. Oral administration of herbals in females may be most common in the population. Such observation is often made in CAM/herbal use prevalence studies [1-3]. It is therefore expected that this population is also overrepresented in all included reports. A higher reporting rate of ADR by females could be another factor contributing to such pattern [25]. On the other hand, a higher proportion of females experiencing an adverse reaction in our study may confirm results of other studies where a higher incidence of hypersensitivity reaction in females compared to males was found [26, 27]. Nevertheless, this finding does not allow conclusions regarding the role of those characteristics as risk factors although they are further discussed in the literature.

Asthma-like reactions were found in 4.8% of reports. Some commonly used herbals display a wide spectrum of cross-reactivity to other common inhalation or food allergens. Therefore a preexisting diagnosis of asthma and other atopic diseases may be a risk factor for the development of allergic

reactions to herbals. There is a relevant incidence of herbal use among patients with known allergies [28]. For example, herbal medicine was shown to be the third popular choice among patients suffering from asthma with a prevalence of 60-70% in patients with a history of moderate or severe asthma in the United Kingdom [29]. These findings imply that in the presence of known atopic diseases health professionals and patients should only use herbals with great care in order to prevent severe allergic reactions to herbals in this special population.

Other relevant factors that were not recorded and could have contributed to the development of allergy-like reactions could have been user's genetics, nutrition status, concurrent medication, disease states (e.g.: food allergies) and exercise induced anaphylaxis. Also, unrecognized herbal-drug interactions could result in a lack of allergy control and manifestation of allergy symptoms.

Strengths of our study include the international collection of reports from 42 countries over more than four decades and the use of standardized HATC drug classification, WHOART nomenclature and formal causality assessment for adverse reactions. At the same time it is important to recognize special characteristics and inherent limitations of this data source for the study design and interpretation of findings. Most important, spontaneous reporting data do not provide information on the actual exposure to herbals in a population or on the incidence of related ADR. Therefore, qualitative descriptive analyses and signal detection for previously unknown drug safety issues are the primary strength of spontaneous reporting systems rather than quantitative analyses. Furthermore, the level of documentation in VigiBase® is heterogeneous, the extracted reports do not contain original detailed free-text descriptions by the primary reporters, and particularly for early reports formal causality assessment may not be available requiring exclusion from our study population. One must also realize that a standardized reaction term has many advantages, but it is not the same as a clinical diagnosis based on established clinical diagnostic criteria [30]. In light of those limitations we used a restrictive study design emphasizing high specificity with regard to the likely diagnosis of immediate-type allergic reactions and consequently excluded the majority of reports from the extracted original raw dataset. Such a conservative approach implies reduced sensitivity for signal detection, but we believe that overall it improves the interpretability of our findings.

There are several other challenges that pharmacovigilance studies investigating risks associated with herbal remedies face in general. As a result of insufficient herbal product regulations, some ADR may

be attributable to a lack of standardization, contamination, adulteration, plant misidentification/substitution, improper use of herbal medicines including their inappropriate labeling rather than pharmacological/toxicology effects of herbals [5-7, 31]. Also, implementation of innovative preparation methods of traditionally used herbal remedies may alter pharmacological/toxicological properties of herbs and lead to their toxicity rather than therapeutic use. In the era of market globalization, the knowledge of traditional preparation and use of herbals is therefore necessary given the increase in use of traditional herbal remedies outside of their culture of origin.

An estimate of the frequency of ADR to herbals is not possible based on analyses of spontaneous reporting data, but we must assume that our findings represent only the "tip of the iceberg" regarding safety issues with herbal remedies [10]. Moreover, underreporting of adverse events particularly herbals by patients as well as health care professionals is high and health care professionals are not always aware of potential safety issues associated with herbal use [8-10, 32, 33].

In summary, any pharmacologically active product including herbal has the potential to cause harm. We found that herbal medicines for oral use carry a risk for allergy-like immediate ADR and that studies using the WHO-UMC pharmacovigilance database can identify specific associations between particular herbals and adverse reactions. As the prevalence of herbal use is increasing, health care professionals as well as patients need to become better informed about the possible risks associated with herbal medicines. When health care professionals take drug histories they should actively ask their patients also about all self-administered herbal remedies and dietary supplements. Further studies are needed to establish associations and risk factors that are related to herbal use and allergic reactions.

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